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Supplementary appendix

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Outcomes of the SARS-CoV-2 omicron (B.1.1.529) variant outbreak among vaccinated and unvaccinated patients with cancer in Europe: results from the retrospective, multicentre, OnCovid registry study.

APPENDIX

CONTENTS

Supplementary Methods

Study design, procedures and statistical analysis

OnCovid (NCT04393974) is an active European registry study that, since the beginning of the pandemic, has collected consecutive patients fulfilling the following inclusion criteria: 1) age ≥18 years; 2) diagnosis of SARS-CoV-2 infection confirmed by RT-PCR of a nasopharyngeal swab; 3) history of solid or hematologic malignancy, at any time during the patients' past medical history, either active or in remission at the time of COVID-19 diagnosis. Patients with a history of non-invasive/premalignant lesions or with low malignant potential (i.e., basal cell carcinoma of the skin, non-invasive carcinoma in situ of the cervix, ductal carcinoma in situ) were excluded. For hematologic malignancies, only patients with a history of oncologic diseases with defined malignant behavior (lymphoma, leukaemia, multiple myeloma) were included.
OnCovid was granted central approval by the United Kingdom Health Research Authority (20/HRA/1608) and by the corresponding research ethics committees at each participating institution. Core study data were collated from electronic medical records into a case report form designed using the Research Electronic Data Capture software (REDCap, Vanderbilt University, Nashville, TN, USA). Multi-site access and data curation was coordinated by the Medical Statistics Unit in Novara, Italy.

The overarching subgrouping of demographics, oncological and COVID-19 related features has been consistently utilised in all the publications from our registry (Cancer Discov. 2020 Jul 31;10(10):1465–74; Eur J Cancer. 2021 Jun;150:190-202; J Immunother Cancer. 2021 Mar;9(3):e002277; Cancers. 2020 Jul 8;12(7):1841; Lancet Oncol. 2021 Nov 3;S1470-2045(21)00573-8; JAMA Oncol. 2021 Nov 24) and was made necessary by the wide heterogeneity oncological diagnoses included in the registry.
By the data lock of 4th of February 2022, the registry included 3820 patients from 37 institutions across 6 countries (UK, Italy, Spain, France, Belgium and Germany), with patients diagnosed with COVID-19 between the 27th of February 2020 and the 31st of January 2022. To ensure consecutive accrual and outcomes comparability, data from centers that did not actively enter new data from the March 2021 data lock was subsequently excluded from the present analysis, resulting in a final population of 3473 patients from 34 institutions across 3 countries (UK, Italy and Spain).

The following key variables were considered as key demographics and tomour characteristics:

- Country (United Kingdom, Spain, Italy),
- Biological sex (male vs female),
- Age (both continuous and categorical: ≥65 vs < 65 years),
- Number of co-morbidities (0-1 vs ≥ 2),
- Smoking status (Never vs ever smokers),
- Primary tumour (clustered as: breast, gastro-intestinal, gynaecological/genito-urinary, thoracic, others, and haematologic),
- Tumour stage (defined as advanced vs non-advanced). In details, we defined as “advanced” stage any patient with distant metastatic disease, to differentiate them from “non-advanced” patients. Disease-specific criteria (i.e. Rai, Binet criteria etc.) were utilised as appropriate to define advanced haematological malignancies.
- Tumour status (presence of active vs non-active disease), on the basis of disease-specific criteria (radiologic, clinical, biochemical/haematological depending on disease type).
- Receipt of systemic anticancer therapy (SACT) within 4 weeks prior to SARS-CoV-2 infection (yes vs no – chemotherapy including combinations regimen vs immune checkpoint inhibitors vs endocrine therapy vs tyrosine kinase inhibitors/monoclonal antibodies/other targeted agents);

The following clinical outcomes were considered as proxy of COVID-19 severity:

- Experience of at least one COVID-19 related symptom including: fever, cough, fatigue, , dyspnoea, anosmia, dysgeusia, coryzal symptoms, diarrhoea, headache, myalgia, nausea/vomiting, sore throat, others (yes vs no);
- Experience of at least one COVID-19 complications including acute respiratory failure, ARDS, kidney injury, secondary infections, sepsis, septic shock, acute cardiac injury, acute liver injury and others (yes vs no);
- Receipt of any COVID-19 oriented therapy, including antivirals, antimalarials, antibiotics, corticosteroids, interleukin-6 inhibitors and others (yes vs no);
- Hospitalization requirement (pre-existent/due to COVID-19 vs not required);
- Oxygen therapy requirement, due to COVID-19 (yes vs no).

The vaccination status of patients for whom the vaccine type was not specified, was categorized considering the traditional vaccination course with two doses prior to COVID-19 defining a full vaccination and a third dose defining the boosted status.

Considering that only mRNA vaccines were approved for booster doses during the study period, the vaccine type of booster doses was not collected.

Oncological and disease specific variables were collected at baseline, defined at the moment of diagnosis of SARS-CoV-2 by PCR test. Characteristics of severity, complications and therapy against COVID-19 were collected throughout the observation period until full clinical resolution of COVID-19 or patients' mortality.

Patient observation time started from date of first PCR/SARS-CoV-2 infection confirmation until patient death or loss to follow-up. Being a retrospective, observational study, the entirety of the OnCovid cohort was followed up at intervals dictated by routine clinical practice at each participating institution, as deemed clinically indicated by the treating physicians. Mortality by all cause was retrieved and validated by investigators at each centre by accessing patients' electronic medical records and death certificates.

Patients were lost to follow-up when for any reason failed to attend planned follow-up appointments scheduled by the treating clinicians. Given the pragmatic nature of this registry, based on standard of care clinical practice, we could not accurately reconstruct the reasons to explain why a proportion of patients did not attend for follow-up. To provide an estimation of the impact of follow-up missingness across the study population, we presented the number of patients with an incomplete follow-up (those marked as censored but with an observation period shorter than 14 days from COVID-19 diagnosis) for each time-phase. To maximize the sample size and considering the larger proportion of incomplete follow-up patients among those diagnosed during the more recent Omicron phase, these patients were considered censored as alive and included in the 14-days and 28-days CFR analyses and the analysis of the risk of death at 28 days. However, patients with missing information for any COVID-19 outcome (nether alive nor death) were excluded from the analysis.

Baseline characteristics were summarized as categorical variables and reported using descriptive statistics. We tested associations between categorical variables using the Fisher exact test and the Pearson $\chi 2$ test as appropriate. COVID-19 outcomes were presented as crude rates with 95% confidence intervals (95%CI).

Each COVID-19 outcome of patients diagnosed during the Alpha-Delta variants phase and the Omicron variant phase were compared to those of patients diagnosed during the pre-vaccination phase using separated fixed multivariable logistic regression models and presented as adjusted odds ratios (aOR) with 95%CI. This approach was adopted to include all variables already known to influence all COVID-19 outcomes presented, as reproducibly established in all prior analyses from the OnCovid registry, in order to account for the unbalanced distribution of patients' characteristics and disease-related features.The following key variables of interest (categorized as above) were used as covariates: country, sex, age (continuous), number of co-morbidities, primary tumour, tumour stage at COVID-19 and tumour status at COVID-19, the receipt of SACT

within 4 weeks of COVID-19 diagnosis. Considering the restricted time-distribution of vaccination rate, SARS-CoV-2 vaccines were not included in the model.

The ancillary analysis of the risk of death at 28 days was performed following the same fixed multivariable modelling using Cox regression, whit results presented as adjusted hazard ratios (aHR) with 95%CI.

To compare the 14-day CFRs of unvaccinated patients across the predefined phases a propensity score matching with 1:3 ratio and a caliper of 0.2 was performed to obtain comparable groups. The balancing ability of the propensity score matching procedures was estimated through the standardized mean differences (SMD) of the matched characteristics.

Subsequently, to evaluate vaccination trends and their effectiveness, we analysed COVID-19 morbidity and mortality at 14 and 28 days, among patients diagnosed from the date of the first SARS-CoV-2 breakthrough infection reported in a boosted patient onwards (17/11/2021). This approach was adopted to ensure comparability of vaccination subgroups, given the already established strong and significant time-dependent changes in demographics, oncological characteristics, and COVID-19 outcomes in patients with cancer. Patients with unknown vaccination status were excluded from the analysis. For the vaccination analysis a two-tiered approach was adopted; we first evaluated COVID-19 outcomes between unvaccinated and vaccinated patients, including all patients who received at least one dose of SARS-CoV-2 vaccine. Second, we explored vaccination subgroups by comparing COVID-19 outcomes between boosted and double-dosed/partially vaccinated patients with unvaccinated patients separately, and then between boosted with double-dosed/partially vaccinated patients.

To optimize this smaller cohort and considering the markedly unbalanced sample size we used the Inverse Probability of Treatment Weighting (IPTW) accounting for selected demographics and oncological characteristics. To obtain a more powered IPTW we included variables with missing data by grouping them as reference term in case of <5% missingness and as an "unknown" category in case of ≥5% missingness. The following covariates were included in the first-tier vaccination analysis: country (United Kingdom vs Spain vs Italy), sex (male vs female), age (≥65 vs <65 years), number of co-morbidities (0-1 vs ≥2), tumour status (presence of active vs non-active disease), tumour stage (advanced vs non-advanced vs unknown) and receipt of SACT at COVID-19 (yes vs no vs unknown). Given the reduction of the sample size, only sex, age, comorbidities and tumour status were included in the IPTW for the second-tier vaccination analysis. The balancing ability of the IPTW was evaluated thought the distribution of the unweighted and weighted selected variables with relevant p-values and SMD. In view of the reduced balancing ability of the IPTW for the second-tier analysis, only an exploratory analysis of the 14-days and 28-days CFRs was performed across the second-tier vaccination subgroups.

For the multivariable analysis propensity score-weighted logistic regression models were then fitted for each COVID-19 outcome of interest, using all the above-mentioned covariates, with results presented as adjusted odds ratios (aOR) and 95%CI. Estimation of variance for the IPTW was performed with a cluster-robust standard error evaluation for each variable included in all multivariable models. Considering that data-source consisted of 33 different institutions, which could represent a source of bias, multivariable models for the main pandemic phases and SARS-CoV-2 vaccination analyses were corrected following a clustered-robust standard error adjustment for participating centre with results presented through corrected 95%CI, and unadjusted and adjusted standard errors and p-values.

Analyses were performed using the R-studio software, R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, and the MedCalc® Statistical Software version 20 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2021).

Supplementary Table 1: Patient disposition across participating centres. PI: principal investigator.

Institution	Total patients		Eligible – omicron outbreak analysis		Eligible – booster analysis		Site PI
	N	%	N	%	N	%	
Vall d'Hebron University Hospital, Barcelona (Spain)	532	13.9	529	15.2	109	26.3	Josep Tabernero
Chelsea and Westminster Hospital, London (UK)	444	11.6	434	12.5	12	2.9	Mark Bower
University College London, London (UK)	377	9.9	347	10.0	43	10.4	Alvin JX Lee
Ospedale Maggiore della Carità, Novara (Italy)	244	6.4	239	6.9	3	0.7	Alessandra Gennari
Barts Health NHS Trust, London (UK)	237	6.2	207	6.0	13	3.1	Nikolaos Diamantis
ICO L'Hospitalet, L'Hospitalet de Llobregat, Barcelona (Spain)	193	5.1	192	5.5	31	7.5	Ramon Salazar
Guy's and St Thomas' NHS Foundation Trust, London (UK)	190	5.0	190	5.5	24	5.8	Ailsa Sita-Lumsden
Institut Gustave Roussy, Villejuif (France)	190	5.0	-	-	-	-	Fanny Pommeret
IRCCS Humanitas Research Hospital, Rozzano - Milan (Italy)	174	4.6	173	5.0	4	1.0	Alexia Bertuzzi
ICO Girona (Spain)	113	3.0	113	3.3	7	1.7	Joan Brunet
Policlinico San Matteo, Pavia (Italy)	109	2.9	108	3.1	12	2.9	Paolo Pedrazzoli
Ospedale Papa Giovanni XXIII, Bergamo (Italy)	107	2.8	107	3.1	-	-	Alberto Zambelli
IRCCS AOU San Martino, Genova (Italy)	95	2.5	87	2.5	18	4.3	Matteo Lambertini
Imperial College London, London (UK)	88	2.3	81	2.3	29	7.0	David J Pinato
Ospedale Antonio e Biagio e Cesare Arrigo, Alessandria (Italy)	82	2.1	76	2.2	4	1.0	Federica Grosso
ICO Badalona (Spain)	79	2.1	78	2.2	16	3.9	Andrea Plaja
Hospital Clinic, Barcelona (Spain)	56	1.5	56	1.6	-	-	Aleix Prat
Manresa Hospital (Spain)	53	1.4	53	1.5	7	1.7	Clara Martinez-Vila
Velindre Cancer Centre, Cardiff (UK)	48	1.3	48	1.4	12	2.9	Sarah Townsend
Careggi University Hospital, Florence (Italy)	36	0.9	36	1.0	18	4.3	Francesca Mazzoni
Ospedali Riuniti di Ancona, Universitá Politecnica delle Marche (Italy)	35	0.9	34	1.0	10	2.4	Rossana Berardi
University of L'Aquila, L'Aquila (Italy)	35	0.9	35	1.0	1	0.2	Alessandro Parisi
Northumbria Healthcare NHS (UK)	35	0.9	35	1.0	15	3.6	Avinash Aujayeb
Institut Jules Bordet, Brussels (Belgium)	30	0.8	-	-	-	-	Angela Loizidou
Azienda Istituti Ospitalieri di Cremona, Cremona (Italy)	28	0.7	27	0.8	2	0.5	Daniele Generali
Università Campus Bio-Medico, Rome (Italy)	26	0.7	26	0.7	3	0.7	Bruno Vincenzi
Azienda Ospedaliera Spedali Civili, Brescia (Italy)	26	0.7	26	0.7	-	-	Salvatore Grisanti
Istituto Europeo di Oncologia, Milano (Italy)	19	0.5	19	0.5	4	1.0	Paola Queirolo
University of Munich (Germany)	19	0.5	-	-	-	-	Nadia Harbeck
Azienda Ospedaliera S. Andrea, Rome (Italy)	18	0.5	18	3.1	4	1.0	Raffaele Giusti
Istituto Tumori, Milan (Italy)	17	0.4	17	0.5	2	0.5	Rossella Bertulli
University of Bari 'Aldo Moro', Bari (Italy)	16	0.4	16	0.5	11	2.7	Marco Tucci
Fondazione Poliambulanza Istituto Ospedaliero, Brescia (Italy)	15	0.4	14	0.4	1	0.2	Michela Libertini
Hospital Universitario 12 de Octubre, Madrid (Spain)	15	0.4	15	0.4	-	-	Ana Sanchez de Torre
Azienda Ospedaliera S Maria, Terni (Italy)	15	0.4	14	0.4	-	-	Annalisa Guida
Santa Maria Goretti Hospital, Latina (Italy)	12	0.3	12	0.3	-	-	Federica Zoratto
Palma de Mallorca Hospital, Palma de Mallorca, (Spain)	4	0.1	4	0.1	-	-	Maria Iglesias
Total	**3820**	**100.0**	**3473**	**100**	**415**	**100**	

Supplementary Table 2: Summary of vaccine type administered according to vaccination category across the overall study population and the population included in the vaccine trend and booster dose analysis.

Overall Population			
	Partially vaccinated N (%)	**Fully vaccinated/double-dosed N (%)**	**Boosted N (%)**
BNT162b2	30 (29.4)	111 (41.9)	88 (47.3)
mRNA-1273	31 (30.4)	48 (18.1)	49 (26.3)
ChAdOx1-S	16 (15.7)	64 (24.2)	32 (17.2)
Ad.26.COV2.S	-	3 (1.1)	3 (1.6)
Not specified	25 (24.5)	39 (14.7)	14 (7.5)
Total	102	265	186
Vaccine trend and booster dose analysis			
	Double-dosed/partially vaccinated N (%)		**Boosted N (%)**
BNT162b2	68 (38.2)		88 (47.3)
mRNA-1273	34 (19.1)		49 (26.3)
ChAdOx1-S	45 (25.3)		32 (17.2)
Ad.26.COV2.S	-		3 (1.6)
Not specified	31 (17.4)		14 (7.5)
Total	178		186

Supplementary Table 3: Multivariable analysis of COVID-19 outcomes across the pre-defined phases of the pandemic. Estimates were computed using a fixed multivariable regression models reporting the aOR with 95%CI corrected according to the clustered-robust adjustment for participating centres. Standard errors and p-values after the clustered-robust adjustment for participating centres are also provided. Adjusting covariates included: country (United Kingdom vs Spain vs Italy), sex (male vs female), age (used as continuous covariate), number of comorbidities (0-1 vs ≥2), primary tumour cluster, stage at COVID-19 (advanced vs non-advanced) and disease status at COVID-19 (remission/non-measurable vs active), receipt of systemic anticancer therapy within 4 weeks from COVID-19. Full models are available as supplementary material (**Supplementary Table 4**). aOR: adjusted odds ratio; CI: confidence intervals; St. Error: standard error.

	Multivariable aOR 95%CI (corrected)	**St. Error; p-value (corrected)**
14-days case fatality rate	2988 patients included	
Pre-vaccination phase	1	
Alpha-Delta phase	0.49 (0.29-0.82)	0.26; 0.001
Omicron phase	0.32 (0.19-0.61)	0.30; <0.001
28-days case fatality rate	2988 patients included	
Pre-vaccination phase	1	
Alpha-Delta phase	0.70 (0.44-1.11)	0.23; 0.13
Omicron phase	0.34 (0.16-0.79)	0.42; 0.012
Complications from COVID-19	3032 patients included	
Pre-vaccination phase	1	
Alpha-Delta phase	0.76 (0.54-1.07)	0.17; 0.12
Omicron phase	0.26 (0.17-0.46)	0.26; <0.0001
Hospitalization due to COVID-19	2267 patients included	
Pre-vaccination phase	1	
Alpha-Delta phase	0.56 (0.39-0.80)	0.18; 0.001
Omicron phase	0.17 (0.09-0.32)	0.31; <0.0001
COVID-19 specific therapy	2804 patients included	
Pre-vaccination phase	1	
Alpha-Delta phase	0.53 (0.36-0.77)	0.19; 0.001
Omicron phase	0.22 (0.15-0.34)	0.19; <0.0001
Oxygen therapy	2805 patients included	
Pre-vaccination phase	1	
Alpha-Delta phase	0.64 (0.50-0.81)	0.12; <0.0001
Omicron phase	0.24 (0.14-0.43)	0.28; <0.0001
COVID-19 symptoms	3032 patients included	
Pre-vaccination phase	1	
Alpha-Delta phase	0.41 (0.28-0.60)	0.19; <0.0001
Omicron phase	0.55 (0.29-0.94)	0.30; 0.05

Supplementary Table 4: Fixed multivariable regression models reporting COVID-19 related outcomes according to the pre-defined phases of the pandemic. Adjusted Odds Ratios are presented with 95%CIs corrected according to the clustered-robust adjustment for participating centres. Standard errors and p-values after the clustered-robust adjustment for participating centres are also provided. *defined as within 4 weeks prior to COVID-19 diagnosis. SACT: systemic anticancer therapy; aOR: adjusted odds ratio; CI: confidence intervals; St. Error: standard error.

	aOR 95%CI (corrected)	St. Error; p-value (corrected)
14-days case fatality rate	2988 patients included	
Pre-vaccination phase	1	
Alpha-Delta phase	0.49 (0.29-0.82)	0.26; 0.001
Omicron phase	0.32 (0.19-0.61)	0.30; <0.001
Country		
United Kingdom	1	
Spain	0.64 (0.42-0.91)	0.19; 0.021
Italy	0.83 (0.56-1.17)	0.18; 0.32
Sex		
Female	1	
Male	1.15 (0.91-1.50)	0.12; 0.26
Age		
Continuous	1.04 (1.03–1.05)	0.005; <0.0001
Number of comorbidities		
0-1	1	
≥ 2	1.43 (1.15-1.80)	0.11; 0.001
Primary tumour		
Breast	1	
Gastro-intestinal	1.22 (0.85-1.60)	0.15; 0.18
Gynaecological/Genito-Urinary	1.09 (0.64-1.64)	0.22; 0.68
Thoracic	1.85 (1.17-2.58)	0.19; 0.001
Others	1.93 (1.14-2.85)	0.22; 0.01
Haematological	1.29 (0.72-2.15)	0.27; 0.344
Tumour stage at COVID-19		
Non-advanced	1	
Advanced	1.78 (1.47-2.20)	0.10; <0.0001
Tumour status at COVID-19		
Remission/non measurable disease	1	
Active malignancy	1.86 (1.52-2.25)	0.09; <0.0001
SACT at COVID-19*		
No	1	
Yes	0.70 (0.58-0.85)	0.09; <0.0001
28-days case fatality rate	2988 patients included	
Pre-vaccination phase	1	
Alpha-Delta phase	0.70 (0.44-1.11)	0.23; 0.13
Omicron phase	0.34 (0.16-0.79)	0.42; 0.012
Country		
United Kingdom	1	
Spain	0.76 (0.53-1.03)	0.16; 0.10
Italy	0.82 (0.56-1.18)	0.18; 0.32
Sex		
Female	1	
Male	1.07 (0.80-1.44)	0.14; 0.61
Age		
Continuous	1.04 (1.03-1.05)	0.004; <0.0001
Number of comorbidities		
0-1	1	
≥ 2	1.54 (1.22-1.96)	0.12; <0.0001
Primary tumour		
Breast	1	
Gastro-intestinal	1.54 (1.09-2.05)	0.15; 0.011
Gynaecological/Genito-Urinary	1.38 (0.79-2.23)	0.25; 0.19
Thoracic	2.21 (1.47-3.12)	0.18; <0.0001
Others	2.20 (1.39-3.33)	0.20; <0.0001
Haematological	1.56 (0.92-2.53)	0.25; 0.08
Tumour stage at COVID-19		
Non-advanced	1	
Advanced	2.08 (1.73-2.53)	0.09; <0.0001
Tumour status at COVID-19		
Remission/non measurable disease	1	
Active malignancy	1.72 (1.38-2.11)	0.10; <0.0001
SACT at COVID-19*		
No	1	
Yes	0.63 (0.53-0.76)	0.09; <0.0001

Complications from COVID-19	3032 patients included	
Pre-vaccination phase	1	
Alpha-Delta phase	0.76 (0.54-1.07)	0.17; 0.12
Omicron phase	0.26 (0.17-0.46)	0.26; <0.0001
Country		
United Kingdom	1	
Spain	1.15 (0.84-1.58)	0.15; 0.33
Italy	0.83 (0.50-1.37)	0.25; 0.48
Sex		
Female	1	
Male	1.35 (1.10-1.61)	0.09; 0.001
Age		
Continuous	1.02 (1.01-1.03)	0.004; <0.0001
Number of comorbidities		
0-1	1	
≥ 2	1.41 (1.24-1.65)	0.07; <0.0001
Primary tumour		
Breast	1	
Gastro-intestinal	1.11 (0.79-1.54)	0.16; 0.52
Gynaecological/Genito-Urinary	1.25 (0.85-1.80)	0.18; 0.23
Thoracic	1.71 (1.18-2.53)	0.19; 0.011
Others	1.22 (0.78-1.94)	0.23; 0.38
Haematological	1.84 (1.36-2.48)	0.15; <0.0001
Tumour stage at COVID-19		
Non-advanced	1	
Advanced	1.18 (0.95-1.44)	0.10; 0.10
Tumour status at COVID-19		
Remission/non measurable disease	1	
Active malignancy	1.12 (0.97-1.29)	0.07; 0.12
SACT at COVID-19*		
No	1	
Yes	0.94 (0.75-1.18)	0.11; 0.64
Hospitalization due to COVID-19	2267 patients included	
Pre-vaccination phase	1	
Alpha-Delta phase	0.56 (0.39-0.80)	0.18; 0.001
Omicron phase	0.17 (0.09-0.32)	0.31; <0.0001
Country		
United Kingdom	1	
Spain	1.25 (0.58-2.69)	0.39; 0.56
Italy	0.51 (0.26-0.95)	0.31; 0.03
Sex		
Female	1	
Male	1.36 (1.06-1.68)	0.12; 0.012
Age		
Continuous	1.03 (1.02-1.04)	0.004; <0.0001
Number of comorbidities		
0-1	1	
≥ 2	1.69 (1.33-2.19)	0.12; <0.0001
Primary tumour		
Breast	1	
Gastro-intestinal	1.13 (0.76-1.73)	0.21; 0.56
Gynaecological/Genito-Urinary	1.62 (1.04-2.58)	0.23; 0.043
Thoracic	1.33 (0.86-2.17)	0.24; 0.23
Others	1.30 (0.73-2.36)	0.29; 0.37
Haematological	2.67 (1.43-5.17)	0.33; 0.011
Tumour stage at COVID-19		
Non-advanced	1	
Advanced	1.19 (0.92-1.56)	0.13; 0.18
Tumour status at COVID-19		
Remission/non measurable disease	1	
Active malignancy	1.02 (0.77-1.35)	0.14; 0.88
SACT at COVID-19*		
No	1	
Yes	0.83 (0.64-1.07)	0.13; 0.17
COVID-19 specific therapy	2804 patients included	
Pre-vaccination phase	1	
Alpha-Delta phase	0.53 (0.36-0.77)	0.19; 0.001
Omicron phase	0.22 (0.15-0.34)	0.19; <0.0001
Country		
United Kingdom	1	
Spain	1.64 (0.73-3.69)	0.40; 0.22
Italy	1.17 (0.53-2.53)	0.39; 0.67
Sex		
Female	1	

Male	1.20 (0.92-1.47)	0.24; 0.14
Age		
Continuous	1.02 (1.01-1.02)	0.004; <0.0001
Number of comorbidities		
0-1	1	
≥ 2	1.12 (0.94-1.39)	0.10; 0.30
Primary tumour		
Breast	1	
Gastro-intestinal	0.91 (0.67-1.32)	0.17; 0.60
Gynaecological/Genito-Urinary	1.11 (0.82-1.60)	0.17; 0.55
Thoracic	1.36 (0.93-2.16)	0.21; 0.14
Others	0.93 (0.59-1.63)	0.26; 0.80
Haematological	3.12 (1.86-5.21)	0.25; <0.0001
Tumour stage at COVID-19		
Non-advanced	1	
Advanced	0.90 (0.71-1.11)	0.10; 0.36
Tumour status at COVID-19		
Remission/non measurable disease	1	
Active malignancy	0.95 (0.77-1.19)	0.11; 0.69
SACT at COVID-19*		
No	1	
Yes	0.99 (0.81-1.21)	0.10; 0.91
Oxygen therapy	2805 patients included	
Pre-vaccination phase	1	
Alpha-Delta phase	0.64 (0.50-0.81)	0.12; <0.0001
Omicron phase	0.24 (0.14-0.43)	0.28; <0.0001
Country		
United Kingdom	1	
Spain	1.64 (1.14-2.34)	0.17; 0.01
Italy	1.19 (0.84-1.64)	0.16; 0.27
Sex		
Female	1	
Male	1.42 (1.19-1.64)	0.08; <0.0001
Age		
Continuous	1.02 (1.01-1.03)	0.006; <0.0001
Number of comorbidities		
0-1	1	
≥ 2	1.40 (1.20-1.67)	0.08; <0.0001
Primary tumour		
Breast	1	
Gastro-intestinal	0.99 (0.65-1.54)	0.22; 0.97
Gynaecological/Genito-Urinary	1.24 (0.86-1.81)	0.18; 0.24
Thoracic	1.59 (1.06-2.47)	0.21; 0.016
Others	1.03 (0.66-1.66)	0.23; 0.87
Haematological	1.88 (1.32-2.71)	0.18; <0.0001
Tumour stage at COVID-19		
Non-advanced	1	
Advanced	1.12 (0.91-1.37)	0.10; 0.26
Tumour status at COVID-19		
Remission/non measurable disease	1	
Active malignancy	0.90 (0.76-1.08)	0.09; 0.26
SACT at COVID-19*		
No	1	
Yes	0.72 (0.61-0.85)	0.08; <0.0001
COVID-19 symptoms	3032 patients included	
Pre-vaccination phase	1	
Alpha-Delta phase	0.41 (0.28-0.60)	0.19; <0.0001
Omicron phase	0.55 (0.29-0.94)	0.30; 0.05
Country		
United Kingdom	1	
Spain	1.59 (0.69-3.90)	0.44; 0.29
Italy	0.69 (0.29-1.62)	0.44; 0.40
Sex		
Female	1	
Male	1.07 (0.84-1.34)	0.12; 0.54
Age		
Continuous	1.01 (1.00-1.02)	0.005; 0.021
Number of comorbidities		
0-1	1	
≥ 2	1.29 (0.92-1.21)	0.17; 0.14
Primary tumour		
Breast	1	
Gastro-intestinal	0.75 (0.54-1.21)	0.21; 0.19
Gynaecological/Genito-Urinary	0.94 (0.67-1.55)	0.24; 0.82
Thoracic	1.26 (0.89-2.12)	0.23; 0.30

Others	0.79 (0.42-1.57)	0.25; 0.01
Haematological	1.93 (1.32-3.36)	0.25; <0.0001
Tumour stage at COVID-19		
Non-advanced	1	
Advanced	0.94 (0.66-1.34)	0.17; 0.76
Tumour status at COVID-19		
Remission/non measurable disease	1	
Active malignancy	0.71 (0.51-0.99)	0.16; 0.033
SACT at COVID-19*		
No	1	
Yes	1.40 (1.06-1.86)	0.14; 0.011

Supplementary Table 5: Fixed multivariable Cox regression model reporting the 28-days risk of death according to the pre-defined phases. *defined as within 4 weeks prior to COVID-19 diagnosis. SACT: systemic anticancer therapy; aHR: adjusted hazard ratio; CI: confidence intervals.

	aHR 95%CI
Risk of death at 28-days	2988 patients included
Pre-vaccination phase	1
Alpha-Delta phase	0.73 (0.62-0.85)
Omicron phase	0.48 (0.34-0.67)
Country	
United Kingdom	1
Spain	0.76 (0.57-1.02)
Italy	0.85 (0.72-1.00)
Sex	
Female	1
Male	1.08 (0.93-1.27)
Age	
Continuous	1.03 (1.02-1.04)
Number of comorbidities	
0-1	1
≥ 2	1.39 (1.19-1.62)
Primary tumour	
Breast	1
Gastro-intestinal	1.43 (1.07-1.90)
Gynaecological/Genito-Urinary	1.28 (0.94-1.73)
Thoracic	1.84 (1.36-2.48)
Others	1.98 (1.37-2.85)
Haematological	1.93 (1.10-1.25)
Tumour stage at COVID-19	
Non-advanced	1
Advanced	1.68 (1.40-2.01)
Tumour status at COVID-19	
Remission/non measurable disease	1
Active malignancy	1.54 (1.28-1.86)
SACT at COVID-19*	
No	1
Yes	0.71 (0.61-0.84)

Supplementary Table 6: summary of COVID-19 outcomes for patients with solid tumours and haematological malignancies across the pre-defined time phases. # Missing values were excluded from denominator in computing COVID-19 outcomes and for any formal subgroups' comparison, however, missing data percentages were computed using the whole reference population. Patients with unknown primary tumour were excluded CI: confidence intervals.. ¥ Clopper-Pearson (exact) binomial CI.

	Prevaccination phase		**Alpha-Delta phase**		**Omicron phase**	
	Solid (N=1714)	**Haematologic (N=310)**	**Solid (N=938)**	**Haematologic (N=124)**	**Solid (N=299)**	**Haematologic (N=63)**
	N (Rate, 95%CI)	**N (Rate, 95%CI)**	**N (Rate, 95%CI)**	**N (Rate, 95%CI)**	**N (Rate, 95%CI)**	**N (Rate, 95%CI)**
Symptoms from COVID-19	1535 (**89.6%**, 88.0-90.9)¥	290 (**93.4%**, 90.2-96.1)¥	750 (**79.9%**, 77.2-82.5)¥	109 (**87.9%**, 80.8-93.1)¥	243 (**81.2%**, 76.4-85.5)¥	59 (**93.6%**, 84.5-98.2)¥
Oxygen therapy Missing #	841 (**53.2%**, 49.6-56.9) 133 (7.8%)	185 (**60.8%**, 52.4-70.2) 6 (1.9%)	367 (**42.2%**, 37.9-46.7) 68 (7.2%)	60 (**50.0%**, 38.2-64.6) 4 (3.2%)	50 (**19.8%**, 14.7-26.2) 47 (15.7%)	21 (**33.9%**, 20.9-51.8) 1 (1.6%)
COVID-19 specific therapy Missing #	986 (**63.2%**, 59.3-67.2) 154 (8.9%)	233 (**78.7%**, 68.9-89.5) 14 (4.5%)	94 (**47.2%**, 42.8-52.0) 60 (6.4%)	74 (**62.2%**, 48.8-78.1) 5 (4.1%)	68 (**25.5%**, 19.8-32.4) 33 (11%)	41 (**65.1%**, 46.7-88.3) -
Complications from COVID-19	663 (**38.6%**, 35.7-41.7)	136 (**43.9%**, 36.8-51.9)	309 (**32.9%**, 29.4-36.9)	50 (**40.3%**, 29.9-53.2)	41 (**13.7%**, 9.8-18.6)	15 (**23.8%**, 13.3-39.3)
Hospitalization Due to COVID-19 Pre-existing Missing #	 947 (**55.7%**, 52.2-59.3) 357 (**20.9%**, 18.9-23.3) 13 (0.7%)	 191 (**62.4%**, 53.8-71.9) 79 (**19.6%**, 14.9-25.2) 4 (1.3%)	 381 (**41.2%**, 37.2-45.5) 290 (**31.3%**, 27.8-35.2) 13 (1.4%)	 53 (**44.1%**, 33.1-57.8) 32 (**26.7%**, 18.2-37.6) 4 (3.2%)	 55 (**18.9%**, 14.2-24.6) 89 (**30.5%**, 24.5-37.6) 8 (2.7%)	 31 (**52.5%**, 35.7-74.6) 5 (**8.4%**, 2.7-19.7) 4 (6.3%)
14-days case fatality rate Missing #	391 (**23.1%**, 20.8-25.5) 19 (1.1%)	73 (**23.6%**, 18.5-29.7) 1 (0.3%)	131 (**14.1%**, 11.8-16.7) 9 (0.9%)	15 (**12.3%**, 6.8-20.3) 2 (1.6%)	29 (**10.4%**, 6.9-14.9) 21 (7%)	2 (**3.1%**, 0.4-11.4) -
28-days case fatality rate Missing #	488 (**28.8%**, 26.3-31.5) 19(1.1%)	34 (**30.4%**, 24.6-37.2) 1 (0.3%)	224 (**24.1%**, 21.1-27.5) 9 (0.9%)	24 (**19.7%**, 12.6-29.3) 2 (1.6%)	42 (**15.1%**, 10.9-20.4) 21 (7%)	3 (**4.7%**, 0.9-13.9) -

Supplementary Table 7: Baseline characteristics of unvaccinated patients across the Alpha-Delta and the Omicron phases. # Missing values were excluded from denominator in computing percentages and for any formal subgroups' comparison, however, missing data percentages were computed using the whole reference population. * Defined as within 4 weeks prior to COVID-19 diagnosis. SACT: systemic anticancer therapy.

	Alpha-Delta phase Unvaccinated	**Omicron phase Unvaccinated**
	N = 659 (%)	**N = 42 (%)**
Country		
United Kingdom	319 (48.4%)	20 (47.6%)
Spain	34 (5.2%)	1 (2.4%)
Italy	306 (46.4%)	21 (50.0%)
Sex		
Female	318 (48.4%)	15 (36.6%)
Male	339 (51.6%)	26 (63.4%)
Missing #	2 (0.3%)	1 (2.4%)
Age		
<65 years	268 (40.9%)	21 (50.0%)
≥65 years	387 (59.1%)	21 (50.0%)
Missing #	4 (0.6%)	-
Comorbidities		
0-1	365 (55.4%)	25 (59.5%)
≥2	294 (44.6%)	17 (40.5%)
Smoking history		
Never smokers	277 (51.3%)	15 (42.9%)
Former/current smokers	263 (48.7%)	20 (57.1%)
Missing #	119 (18.1%)	7 (16.7%)
Primary Tumour		
Breast	100 (15.4%)	3 (7.1%)
Gastrointestinal	161 (24.7%)	15 (35.7%)
Gynaecological/Genito-Urinary	146 (22.4%)	10 (23.8%)
Thoracic	108 (16.6%)	9 (21.4%)
Others	54 (8.3%)	2 (4.8%)
Haematological	82 (12.6%)	3 (7.1%)
Missing #	8 (1.2%)	-
Tumour stage		
Non-advanced	287 (47.2%)	13 (33.3%)
Advanced	321 (52.8%)	26 (66.7%)
Missing #	51 (0.8%)	3 (7.1%)
Status at COVID-19 diagnosis		
Remission/non-measurable	296 (45.1%)	13 (31.7%)
Active malignancy	360 (54.9%)	28 (68.3%)
Missing #	3 (0.4%)	1 (2.4%)
SACT at COVID-19 diagnosis*		
No	359 (57.7%)	20 (54.1%)
Yes	263 (42.3%)	17 (45.9%)
Missing #	37 (5.6%)	5 (11.9%)

Supplementary Table 8: summary of COVID-19 outcomes for vaccinated and unvaccinated patients across the Alpha-Delta and Omicron phases. # Missing values were excluded from denominator in computing COVID-19 outcomes and for any formal subgroups' comparison, however, missing data percentages were computed using the whole reference population. CI: confidence intervals. ¥ Clopper-Pearson (exact) binomial CI.

	Alpha-Delta Vaccinated (N=256)	**Omicron Vaccinated (N=297)**	**Alpha-Delta Unvaccinated (N=659)**	**Omicron Unvaccinated (N=42)**
	N (Rate, 95%CI)	**N (Rate, 95%CI)**	**N (Rate, 95%CI)**	**N (Rate, 95%CI)**
Symptoms from COVID-19	207 (**80.8%**, 75.5-85.5)¥	246 (**82.8%**, 78.1-86.9)¥	541 (**82.1%,** 78.9-85.9)¥	38 (**90.4%,** 77.4-97.3)¥
Oxygen therapy Missing #	88 (**37.3%**, 29.9-45.9) 20 (7.8%)	54 (**20.8%**, 15.6-27.1) 37 (12.4%)	283 (**45.8%**, 40.6-51.5) 42 (6.4%)	14 (**38.9%**, 21.2-65.2) 6 (14.8%)
COVID-19 specific therapy Missing #	94 (**38.8%**, 31.4-47.5) 14 (5.5%)	87 (**31.8%**, 25.5-39.3) 24 (8.1%)	331 (**53.5%**, 47.9-59.6) 41 (6.2%)	18 (**48.6%**, 28.8-76.8) 5 (11.9%)
Complications from COVID-19	79 (**30.8%**, 24.4-38.4)	41 (**13.8%**, 9.9-18.7)	237 (**35.9%**, 31.5-40.8)	13 (**30.9%**, 16.5-52.9)
Hospitalization Due to COVID-19 Pre-existing Missing #	 104 (**41.4%**, 33.8-50.2) 65 (**25.9%**, 19.9-33.0) 5 (1.9%)	 66 (**23.1%**, 17.8-29.3) 79 (**27.6%**, 21.8-34.4) 11 (3.7%)	 266 (**40.8%**, 36.0-46.0) 225 (**34.5%**, 30.1-39.3) 7 (1.1%)	 18 (**42.8%**, 25.4-67.7) 10 (**23.8%**, 11.4-43.7) -
14-days case fatality rate Missing #	22 (**8.5%**, 5.3-13.0) -	21 (**7.4%**, 4.6-11.3) 15 (5.1%)	114 (**17.4%**, 14.3-20.8) 3 (0.5%)	10 (**25.0%,** 11.9-45.9) 2 (4.8%)
28-days case fatality rate Missing #	44 (**17.2%**, 12.5-23.1) -	34 (**12.1%**, 8.3-16.8) 15 (5.1%)	184 (**28.0%**, 24.1-32.4) 3 (0.5%)	11 (**27.5%**, 13.7-49.2) 2 (4.8%)

Supplementary Table 9: Summary of baseline characteristics' distribution after the propensity score matching between unvaccinated patients from the Omicron phase and patients from the Pre-vaccination phase and between unvaccinated patients from the Omicron and Alpha-Delta phases. Variability of included characteristics is estimate through the standardized mean difference (SMD). *defined as within 4 weeks prior to COVID-19 diagnosis SACT: systemic anticancer therapy.

Unvaccinated patients Omicron (N=42)	**Matched 122 patients Pre-vaccination**	**Matched 121 unvaccinated patients Alpha-Delta**
	SMD	**SMD**
Country		
United Kingdom	-0.13	0.08
Spain	0.16	0.05
Italy	0.08	-0.10
Sex	-0.02	0.04
Age (≥ vs < 65 years)	-0.10	-0.09
Comorbidities	-0.08	0.14
Primary Tumour		
Breast	-0.09	-0.06
Gastrointestinal	0.12	0.18
Gynaecological/Genito-Urinary	-0.11	0.04
Thoracic	0.04	-0.14
Others	0.07	-0.22
Haematological	-0.06	0.06
Tumour stage		
Non-advanced	0.12	0.21
Advanced	-0.02	-0.26
Missing	-0.18	0.12
Status at COVID-19 diagnosis	0.07	0.13
SACT at COVID-19 diagnosis*		
No	0.05	-0.08
Yes	-0.13	-0.07
Missing	0.12	-0.19

Supplementary Table 10: Distribution of baseline characteristics according to the vaccination status of the population diagnosed with COVID-19 from the 17th Nov 2022 onwards, included in the vaccines analysis. 32 patients with unknown vaccination status excluded. # Missing values were excluded from denominator in computing percentages and for any formal subgroups' comparison, however, missing data percentages were computed using the whole reference population. * Defined as within 4 weeks prior to COVID-19 diagnosis. SACT: systemic anticancer therapy; ICI: immune checkpoint inhibitors; TKi: tyrosine kinase inhibitor; MAB: monoclonal antibody.

	Overall population	**Unvaccinated**	**Doble-dosed/partially vaccinated**	**Boosted**	**P value**
	N = 415 (%)	**N = 51 (%)**	**N = 178 (%)**	**N = 186 (%)**	
Country					
United Kingdom	148 (35.7%)	22 (43.1%)	78 (43.8%)	48 (25.8%)	0.0003
Spain	170 (41.0%)	17 (33.3%)	74 (41.6%)	79 (42.5%)	
Italy	97 (23.4%)	12 (23.5%)	26 (14.6%)	59 (31.7%)	
Sex					
Female	205 (46.0%)	23 (45.7%)	95 (46.8%)	87 (46.8%)	0.30
Male	206 (54.0%)	27 (54.3%)	80 (53.2%)	99 (50.1%)	
Missing #	4 (0.9%)	1 (1.9%)	3 (1.7%)	-	
Age					
<65 years	199 (48.7%)	26 (52.0%)	91 (52.3%)	82 (44.3%)	0.28
≥65 years	210 (51.3%)	24 (48.0%)	83 (47.7%)	103 (55.7%)	
Missing #	6 (1.4%)	1 (1.9%)	4 (2.2%)	1 (0.5%)	
Comorbidities					
0-1	253 (61.0%)	32 (62.7%)	110 (61.8%)	111 (59.7%)	0.88
≥2	162 (39.0%)	19 (37.3%)	68 (38.2%)	75 (40.3%)	
Smoking history					
Never smokers	147 (43.1%)	16 (39.0%)	64 (44.1%)	67 (43.2%)	0.84
Former/current smokers	194 (56.9%)	25 (61.0%)	81 (55.9%)	88 (56.8%)	
Missing #	74 (17.8%)	10 (19.6%)	33 (18.5%)	31 (16.7%)	
Primary Tumour					
Breast	67 (16.3%)	5 (9.8%)	31 (17.6%)	31 (16.8%)	0.016
Gastrointestinal	112 (27.2%)	17 (33.3%)	50 (28.4%)	45 (24.3%)	
Gynaecological/Genito-Urinary	50 (12.1%)	11 (21.6%)	23 (13.1%)	16 (8.6%)	
Thoracic	81 (19.7%)	10 (19.6%)	32 (18.2%)	39 (21.1%)	
Others	25 (6.1%)	2 (3.9%)	16 (9.1%)	7 (3.8%)	
Haematological	77 (18.7%)	6 (11.8%)	24 (13.6%)	47 (25.4%)	
Missing #	3 (0.7%)	-	2 (1.1%)	1 (0.5%)	
Tumour stage					
Non-advanced	153 (40.7%)	16 (34.8%)	71 (43.0%)	66 (40.0%)	0.58
Advanced	223 (59.3%)	30 (65.2%)	94 (57.0%)	99 (60.0%)	
Missing #	39 (9.4%)	5 (9.8%)	13 (1.7%)	21 (11.3%)	
Status at COVID-19 diagnosis					
Remission/non measurable	153 (37.0%)	16 (32.0%)	66 (37.1%)	71 (38.4%)	0.70
Active malignancy	260 (63.0%)	34 (68.0%)	112 (62.9%)	114 (61.6%)	
Missing #	2 (0.5%)	1 (1.9%)	-	1 (0.5%)	
SACT at COVID-19 diagnosis*					
No	181 (47.8%)	23 (51.1%)	84 (53.2%)	74 (42.0%)	0.11
Yes	198 (52.2%)	22 (48.9%)	74 (46.8%)	102 (58.0%)	
Chemotherapy (± combos)	110 (29.0%)	15 (33.3%)	44 (27.8%)	51 (29.0%)	0.77
ICI only regimens	22 (5.8%)	2 (4.4%)	6 (3.8%)	14 (8.0%)	0.24
Endocrine therapy	15 (4.0%)	3 (6.7%)	7 (4.4%)	5 (2.8%)	0.46
TKIs and MABs and others	51 (13.5%)	2 (4.4%)	17 (10.8%)	32 (18.2%)	0.023
Missing #	36 (8.7%)	6 (11.8%)	20 (11.2%)	10 (5.4%)	

Supplementary Table 11: Distribution of baseline characteristics before and after the IPTW procedure between unvaccinated and vaccinated patients included in the vaccination analysis. Variability of included characteristics is estimated through the standardized mean difference (SMD). * Defined as within 4 weeks prior to COVID-19 diagnosis SACT: systemic anticancer therapy.

	Unvaccinated (%)	Vaccinated (%)	P value	SMD	Unvaccinated Weighted (%)	Vaccinated Weighted (%)	P value	SMD Weighted
Country								
United Kingdom	43.1	34.6	0.41	0.07	35.7	35.7	0.97	0.03
Spain	33.3	42.0			42.2	41.0		
Italy	23.5	23.4			22.1	23.3		
Sex								
Male	52.9	49.2	0.72	0.08	48.1	49.6	0.84	0.04
Age								
≥65 years	47.1	51.1	0.69	0.19	48.3	50.5	0.77	0.03
Comorbidities								
≥2	37.3	39.3	0.90	0.04	36.2	39.0	0.71	0.05
Status at COVID-19								
Active malignancy	66.7	62.1	0.63	0.09	64.2	62.7	0.84	0.03
Tumour stage								
Non-advanced	31.4	37.6	0.68	0.13	31.6	37.5	0.69	0.13
Advanced	58.8	53.0			59.5	53.1		
Unknown	9.8	9.3			8.9	9.5		
SACT at COVID-19*								
No	45.1	43.4	0.63	0.13	48.4	43.4	0.78	0.10
Yes	43.1	48.4			43.2	48.0		
Unknown	11.8	8.2			8.4	8.6		

Supplementary Table 12: Full fitted multivariable logistic regression models after the Inverse Probability of Treatment Weighting (IPTW) procedure for each COVID-19 related outcome comparing all vaccinated patients and unvaccinated patients. The reported aOR and 95%CIs are corrected according to the clustered-robust adjustment for participating centres. Estimation of variance for the IPTW following the cluster-robust standard error evaluation for each variable is also provided. * Defined as within 4 weeks prior to COVID-19 diagnosis SACT: systemic anticancer therapy; UK: United Kingdom; Unk: unknown; aOR: adjusted odds ratio; CI: confidence intervals; Est: estimate of variance; St. Err: standard error.

14-days Case Fatality Rate, 398 patients	**aOR**	**95%CI**		**Est. (St. Err)**
Vaccination status: Any vaccination vs none	0.16	0.06	0.43	-0.17 (0.06)
Country: Italy vs UK	1.04	0.20	5.21	0.01 (0.07)
Country: Spain vs UK	0.53	0.12	2.31	-0.04 (0.06)
Biological sex: male vs female	0.39	0.15	0.99	-0.09 (0.06)
Age: ≥ 65 vs < 65 years	1.46	0.58	3.68	0.05 (0.07)
Comorbidities: ≥2 vs 0-1	4.78	1.45	15.73	0.14 (0.07)
Tumour status at COVID-19: active vs remission	7.11	3.58	14.12	0.14 (0.06)
Tumour stage at COVID-19: Advanced vs Non-advanced	1.51	0.49	4.64	0.04 (0.08)
Tumour stage at COVID-19: Unk vs Non-advanced	1.65	0.10	27.2	0.02 (0.12)
SACT at COVID-19: Yes vs No *	0.92	0.38	2.23	-0.05 (0.08)
SACT at COVID-19: Unk vs No *	0.03	0.01	0.17	-0.20 (0.08)
28-days Case Fatality Rate, 398 patients	**aOR**	**95%CI**		**Est. (St. Err)**
Vaccination status: Any vaccination vs none	0.26	0.09	0.73	-0.16 (0.07)
Country: Italy vs UK	1.44	0.44	4.66	0.06 (0.08)
Country: Spain vs UK	0.46	0.12	1.66	-0.03 (0.08)
Biological sex: male vs female	0.41	0.16	1.06	-0.12 (0.06)
Age: ≥ 65 vs < 65 years	2.49	0.99	6.21	0.12 (0.07)
Comorbidities: ≥2 vs 0-1	2.69	1.14	6.30	0.11 (0.07)
Tumour status at COVID-19: active vs remission	5.65	1.99	15.9	0.17 (0.07)
Tumour stage at COVID-19: Advanced vs Non-advanced	2.24	0.89	5.60	0.09 (0.07)
Tumour stage at COVID-19: Unk vs Non-advanced	1.27	0.12	12.7	-0.02 (0.13)

SACT at COVID-19: Yes vs No *	0.66	0.30	1.41	-0.10 (0.08)
SACT at COVID-19: Unk vs No *	0.15	0.05	0.45	-0.21 (0.10)
Complications from COVID-19, 415 patients	**aOR**	**95%CI**		**Est. (St. Err)**
Vaccination status: Any vaccination vs none	0.30	0.17	0.53	-0.18 (0.07)
Country: Italy vs UK	1.30	0.60	2.79	0.04 (0.09)
Country: Spain vs UK	0.23	0.04	1.28	-0.13 (0.08)
Biological sex: male vs female	0.48	0.27	0.87	-0.10 (0.07)
Age: ≥ 65 vs < 65 years	1.93	0.98	3.77	0.10 (0.08)
Comorbidities: ≥2 vs 0-1	3.61	1.62	8.04	0.19 (0.08)
Tumour status at COVID-19: active vs remission	0.82	0.40	1.68	-0.02 (0.08)
Tumour stage at COVID-19: Advanced vs Non-advanced	2.39	1.16	4.93	0.11 (0.08)
Tumour stage at COVID-19: Unk vs Non-advanced	1.16	0.35	3.82	0.03 (0.13)
SACT at COVID-19: Yes vs No *	1.06	0.35	3.20	-0.01 (0.08)
SACT at COVID-19: Unk vs No *	0.59	0.12	2.77	-0.07 (0.13)
Hospitalization due to COVID-19 (vs not required), 291 patients	**aOR**	**95%CI**		**Est. (St. Err)**
Vaccination status: Any vaccination vs none	0.34	0.19	0.64	-0.21 (0.09)
Country: Italy vs UK	0.87	0.31	2.44	-0.03 (0.10)
Country: Spain vs UK	0.07	0.01	0.36	-0.44 (0.11)
Biological sex: male vs female	0.47	0.26	0.84	-0.13 (0.08)
Age: ≥ 65 vs < 65 years	3.27	1.32	8.07	0.22 (0.09)
Comorbidities: ≥2 vs 0-1	1.15	0.42	3.12	0.03 (0.09)
Tumour status at COVID-19: active vs remission	1.22	0.64	2.35	0.02 (0.09)
Tumour stage at COVID-19: Advanced vs Non-advanced	1.80	0.57	5.65	0.09 (0.10)
Tumour stage at COVID-19: Unk vs Non-advanced	0.98	0.26	3.65	-0.01 (0.17)
SACT at COVID-19: Yes vs No *	1.34	0.39	4.53	0.05 (0.10)
SACT at COVID-19: Unk vs No *	1.03	0.35	2.99	0.03 (0.13)
COVID-19 specific therapy (vs not required), 379 patients	**aOR**	**95%CI**		**Est. (St. Err)**
Vaccination status: Any vaccination vs none	0.45	0.22	0.92	-0.17 (0.09)
Country: Italy vs UK	1.83	0.50	6.64	0.14 (0.10)
Country: Spain vs UK	0.58	0.14	2.41	-0.10 (0.13)
Biological sex: male vs female	0.86	0.47	1.57	-0.04 (0.08)
Age: ≥ 65 vs < 65 years	1.86	1.02	3.39	0.14 (0.09)
Comorbidities: ≥2 vs 0-1	1.08	0.43	2.72	0.01 (0.09)
Tumour status at COVID-19: active vs remission	1.10	0.42	2.89	0.02 (0.10)
Tumour stage at COVID-19: Advanced vs Non-advanced	1.37	0.46	4.03	0.07 (0.11)
Tumour stage at COVID-19: Unk vs Non-advanced	3.20	0.64	16.03	0.26 (0.14)
SACT at COVID-19: Yes vs No *	0.94	0.46	1.88	-0.02 (0.10)
SACT at COVID-19: Unk vs No *	0.56	0.21	1.51	-0.12 (0.15)
Oxygen therapy (vs not required), 365 patients	**aOR**	**95%CI**		**Est. (St. Err)**
Vaccination status: Any vaccination vs none	0.29	0.18	0.46	-0.20 (0.08)
Country: Italy vs UK	3.57	1.33	9.54	0.23 (0.09)
Country: Spain vs UK	0.38	0.07	2.09	-0.09 (0.10)
Biological sex: male vs female	0.39	0.19	0.78	-0.15 (0.07)
Age: ≥ 65 vs < 65 years	3.68	1.79	7.53	0.22 (0.08)
Comorbidities: ≥2 vs 0-1	1.53	0.61	3.87	0.06 (0.08)
Tumour status at COVID-19: active vs remission	0.86	0.41	1.79	-0.00 (0.09)
Tumour stage at COVID-19: Advanced vs Non-advanced	1.24	0.55	2.82	0.03 (0.09)
Tumour stage at COVID-19: Unk vs Non-advanced	0.36	0.07	1.69	-0.17 (0.16)
SACT at COVID-19: Yes vs No *	0.53	0.32	0.87	-0.11 (0.09)
SACT at COVID-19: Unk vs No *	0.49	0.19	1.25	-0.14 (0.13)

Supplementary Table 13: Distribution of baseline characteristics before and after the IPTW procedure between unvaccinated and boosted patients, unvaccinated and double-dosed/partially vaccinated patients, and between boosted and double-dosed/partially vaccinated patients. Variability of included characteristics is estimated through the standardized mean difference (SMD).

	Unvaccinated (%)	Boosted (%)	P value	SMD	Unvaccinated Weighted (%)	Boosted Weighted (%)	P value	SMD Weighted
Sex								
Male	52.9	53.2	1.00	0.00	48.1	53.7	0.48	0.11
Age								
≥65 years	47.1	55.4	0.37	0.16	48.3	54.8	0.42	0.12
Comorbidities								
≥2	37.3	40.3	0.81	0.06	36.2	39.9	0.64	0.07
Status at COVID-19								
Active malignancy	66.7	61.3	0.59	0.11	64.2	61.9	0.77	0.04
	Unvaccinated (%)	**Double-dose/partial (%)**	**P value**	**SMD**	**Unvaccinated Weighted (%)**	**Double-dose/partial Weighted (%)**	**P value**	**SMD Weighted**
Sex								
Male	52.9	44.2	0.39	0.16	48.1	45.3	0.73	0.05
Age								
≥65 years	47.1	46.6	1.00	0.00	48.3	46.1	0.78	0.04
Comorbidities								
≥2	37.3	38.2	1.0	0.01	36.2	38.1	0.81	0.03
Status at COVID-19								
Active malignancy	66.7	62.9	0.74	0.07	64.2	63.5	0.93	0.01
	Double-dose/partial (%)	**Boosted (%)**	**P value**	**SMD**	**Double-dose/partial Weighted (%)**	**Boosted Weighted (%)**	**P value**	**SMD Weighted**
Sex								
Male	44.9	53.2	0.14	0.16	45.3	53.7	0.11	0.16
Age								
≥65 years	46.6	55.4	0.11	0.17	46.1	54.8	0.09	0.17
Comorbidities								
≥2	38.2	40.3	0.75	0.04	38.1	39.9	0.72	0.03
Status at COVID-19								
Active malignancy	62.9	61.3	0.83	0.03	63.5	61.9	0.75	0.03

Supplementary Table 14: Full fitted multivariable logistic regression models after the Inverse Probability of Treatment Weighting (IPTW) procedure for the 14-days and 28-days case fatality rates comparing unvaccinated and boosted patients, unvaccinated and double-dosed/partially vaccinated patients, boosted and double-dosed/partially vaccinated patients. Estimation of variance for the IPTW following the cluster-robust standard error evaluation for each variable is also provided. *Defined as within 4 weeks prior to COVID-19 diagnosis SACT: systemic anticancer therapy; UK: United Kingdom; Unk: unknown; aOR: adjusted odds ratio; CI: confidence intervals; Est: estimate of variance; St. Err: standard error.

14-days Case Fatality Rate, 226 patients	**aOR**	**95%CI**		**Est. (St. Err)**
Vaccination status: Boosted vs none	-	-	-	-
Country: Italy vs UK	-	-	-	-
Country: Spain vs UK	-	-	-	-
Biological sex: male vs female	-	-	-	-
Age: ≥ 65 vs < 65 years	-	-	-	-
Comorbidities: ≥2 vs 0-1	-	-	-	-
Tumour status at COVID-19: active vs remission	-	-	-	-
Tumour stage at COVID-19: Advanced vs Non-advanced	-	-	-	-
Tumour stage at COVID-19: Unk vs Non-advanced	-	-	-	-
SACT at COVID-19: Yes vs No *	-	-	-	-
SACT at COVID-19: Unk vs No *	-	-	-	-
28-days Case Fatality Rate, 226 patients	**aOR**	**95%CI**		**Est. (St. Err)**
Vaccination status: Boosted vs none	0.20	0.11	0.38	-0.16 (0.07)
Country: Italy vs UK	1.36	0.76	2.45	0.05 (0.08)
Country: Spain vs UK	0.49	0.19	1.25	-0.03 (0.08)

Biological sex: male vs female	0.45	0.26	0.79	-0.10 (0.07)
Age: ≥ 65 vs < 65 years	2.22	1.23	4.03	0.10 (0.07)
Comorbidities: ≥2 vs 0-1	3.23	1.78	5.88	0.11 (0.08)
Tumour status at COVID-19: active vs remission	4.37	2.01	9.47	0.13 (0.06)
Tumour stage at COVID-19: Advanced vs Non-advanced	2.76	1.31	5.08	0.11 (0.07)
Tumour stage at COVID-19: Unk vs Non-advanced	1.30	0.46	3.70	-0.03 (0.11)
SACT at COVID-19: Yes vs No *****	0.83	0.46	1.49	-0.10 (0.07)
SACT at COVID-19: Unk vs No*****	0.04	0.01	0.29	-0.26 (0.11)
14-days Case Fatality Rate, 221 patients	**aOR**	**95%CI**		**Est. (St. Err)**
Vaccination status: Double-dose/partial vs none	0.17	0.8	0.34	-0.15 (0.06)
Country: Italy vs UK	1.05	0.54	2.02	0.02 (0.08)
Country: Spain vs UK	0.62	0.18	2.06	-0.02 (0.08)
Biological sex: male vs female	0.36	0.19	0.70	-0.10 (0.06)
Age: ≥ 65 vs < 65 years	1.52	0.79	2.91	0.07 (0.07)
Comorbidities: ≥2 vs 0-1	4.90	2.44	9.81	0.14 (0.07)
Tumour status at COVID-19: active vs remission	5.49	2.01	14.96	0.12 (0.06)
Tumour stage at COVID-19: Advanced vs Non-advanced	2.27	0.98	5.26	0.06 (0.07)
Tumour stage at COVID-19: Unk vs Non-advanced	2.14	0.63	7.16	0.02 (0.12)
SACT at COVID-19: Yes vs No *****	0.85	0.43	1.65	-0.07 (0.07)
SACT at COVID-19: Unk vs No *****	0.07	0.01	0.43	-0.22 (0.08)
28-days Case Fatality Rate, 221 patients	**aOR**	**95%CI**		**Est. (St. Err)**
Vaccination status: Double-dose/partial vs none	0.29	0.15	0.53	-0.14 (0.06)
Country: Italy vs UK	1.61	0.89	2.91	0.09 (0.08)
Country: Spain vs UK	0.53	0.16	1.75	-0.01 (0.09)
Biological sex: male vs female	0.41	0.23	0.75	-0.13 (0.06)
Age: ≥ 65 vs < 65 years	2.95	1.62	5.37	0.18 (0.07)
Comorbidities: ≥2 vs 0-1	2.79	1.52	5.15	0.10 (0.07)
Tumour status at COVID-19: active vs remission	4.76	1.98	11.42	0.14 (0.06)
Tumour stage at COVID-19: Advanced vs Non-advanced	2.54	1.20	5.39	0.09 (0.07)
Tumour stage at COVID-19: Unk vs Non-advanced	1.39	0.44	4.38	-0.03 (0.13)
SACT at COVID-19: Yes vs No *****	0.68	0.37	1.25	-0.12 (0.07)
SACT at COVID-19: Unk vs No *****	0.21	0.07	0.61	-0.24 (0.10)
14-days Case Fatality Rate, 349 patients	**aOR**	**95%CI**		**Est. (St. Err)**
Vaccination status: Boosted vs Double-dose/partial	0.97	0.52	1.81	-0.01 (0.03)
Country: UK vs Italy	1.88	0.92	3.86	0.05 (0.03)
Country: UK vs Spain	0.33	0.07	1.49	-0.03 (0.03)
Biological sex: male vs female	0.91	0.49	1.68	-0.01 (0.03)
Age: ≥ 65 vs < 65 years	2.61	1.24	5.46	0.05 (0.03)
Comorbidities: ≥2 vs 0-1	1.09	0.55	2.13	0.01 (0.03)
Tumour status at COVID-19: active vs remission	1.83	0.80	4.17	0.04 (0.03)
Tumour stage at COVID-19: Advanced vs Non-advanced	1.48	0.67	3.27	0.02 (0.03)
Tumour stage at COVID-19: Unk vs Non-advanced	1.15	0.34	3.85	-0.01 (0.05)
SACT at COVID-19: Yes vs No *****	0.71	0.36	1.41	-0.03 (0.03)
SACT at COVID-19: Unk vs No *****	0.31	0.07	1.28	-0.07 (0.05)
28-days Case Fatality Rate, 211 patients	**aOR**	**95%CI**		**Est. (St. Err)**
Vaccination status: Boosted vs Double-dose/partial	0.90	0.53	1.52	-0.02 (0.03)
Country: UK vs Italy	3.13	1.68	5.81	0.13 (0.04)
Country: UK vs Spain	0.55	0.17	1.79	-0.00 (0.04)
Biological sex: male vs female	0.69	0.41	1.15	-0.04 (0.03)
Age: ≥ 65 vs < 65 years	3.43	1.83	6.41	0.10 (0.03)
Comorbidities: ≥2 vs 0-1	1.26	0.73	2.17	0.03 (0.04)
Tumour status at COVID-19: active vs remission	1.95	0.97	3.91	0.06 (0.03)
Tumour stage at COVID-19: Advanced vs Non-advanced	2.27	1.17	4.39	0.07 (0.04)
Tumour stage at COVID-19: Unk vs Non-advanced	0.91	0.28	2.96	-0.03 (0.05)
SACT at COVID-19: Yes vs No *****	0.58	0.32	1.05	-0.06 (0.04)
SACT at COVID-19: Unk vs No *****	0.96	0.42	2.18	-0.01 (0.08)

Supplementary Table 15: Summary of COVID-19 outcomes for patients with solid tumours and haematological malignancies according to their vaccination status from the vaccination analysis. # Missing values were excluded from denominator in computing COVID-19 outcomes and for any formal subgroups' comparison, however, missing data percentages were computed using the whole reference population. CI: confidence intervals. Patients with unknown primary tumour were excluded. ¥ Clopper-Pearson (exact) binomial CI.

	Unvaccinated		**Vaccinated**	
	Solid (N=45)	**Haematologic (N=6)**	**Solid (N=290)**	**Haematologic (N=71)**
	N (Rate, 95%CI)	**N (Rate, 95%CI)**	**N (Rate, 95%CI)**	**N (Rate, 95%CI)**
Symptoms from COVID-19	39 (**86.7%**, 73.2-94.9)¥	6 (**100%**, 54.1-100)¥	228 (**77.8%**, 73.4-83.2)¥	65 (**91.5%**, 82.5-96.8)¥
Oxygen therapy	15 (**38.5%**, 21.5-63.4)	3 (**50.0%**, 11.8-88.2)¥	47 (**18.7%**, 13.7-24.9)	22 (**31.8%**, 19.9-48.2)
Missing #	6 (13.3%)	-	42 (14.5%)	2 (2.8%)
COVID-19 specific therapy	18 (**45.0%**, 26.7-71.1)	4 (**8.0%**, 22.2-95.7)¥	64 (**24.3%**, 18.7-31.1)	43 (**60.5%**, 43.8-81.6)
Missing #	5 (11.1%)	1 (16.6%)	30 (10.3%)	-
Complications from COVID-19	14 (**31.1%**, 17.0-52.2)	2 (**33.3%**, 4.3-77.7)¥	38 (**12.9%**, 9.1-17.8)	17 (**23.9%**, 13.9-38.3)
Hospitalization				
Due to COVID-19	19 (**42.2%**, 25.4-65.9)	2 (**33.3%**, 4.3-77.7)¥	51 (**17.8%**, 13.3-23.4)	31 (**48.4%**, 32.9-68.7)
Pre-existing	11 (**24.4%**, 12.2-43.7)	2 (**33.3%**, 4.3-77.7)¥	91 (**31.8%**, 25.6-39.1)	6 (**9.4%**, 3.4-20.4)
Missing #	-	-	7 (2.4%)	7 (9.9%)
14-days case fatality rate	11 (**25.6%**, 12.7-45.8)	-	22 (**7.9%**, 4.9-11.9)	2 (**2.8%**, 0.3-10.1)
Missing #	2 (4.4%)		15 (5.2%)	-
28-days case fatality rate	13 (**30.2%**, 16.1-51.7)	-	37 (**13.3%**, 9.4-18.3)	4 (**5.6%**, 1.5-14.4)
Missing #	2 (4.4%)		15 (5.2%)	-